BOX PATENT EXT.
PATENT
2294-0116M

IN THE U.S. PATENT AND TRADEMARK OFFICE

Patent No.: 5,135,943

Issued: August 4, 1992

Assignee: Ferrer Internacional S.A.

For: 1H-IMIDAZOLE DERIVATIVE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

February 5, 2004

Sir:

The applicant, FERRER INTERNACIONAL, S.A., of Barcelona Spain, represents that it is the assignee of the entire interest in and to Letters Patent for the United States 5,135,943 granted to Rafael Foguet[1], Marcial Moreno, Manuel Raga, Rosa M. Cuberes, Jose M. Castello, and Jose A. Ortiz, on August 4, 1992 for 1H-IMIDAZOLE DERIVATIVE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME by virtue of an Assignment in favor of FERRER INTERNACIONAL, S.A. recorded on February 1, 1991, at Reel/Frame 005625/0795. The applicant, acting through its duly authorized attorney whose power to act on behalf of applicant is

[1] A Petition to remove inventor Rafael Foguet was filed on June 16, 2003 (see Exhibit 2).

filed simultaneously herewith (Exhibit 1), hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information required by 37 C.F.R. §1.740.

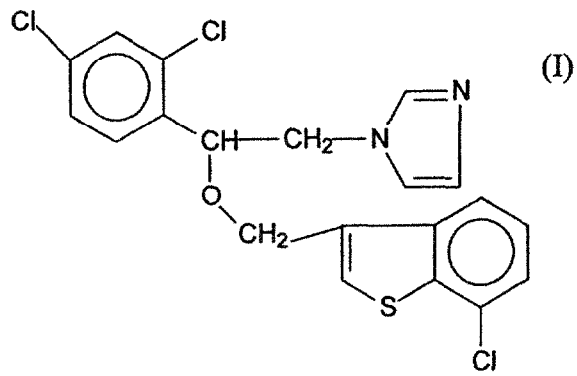
The applicant for patent term extension, FERRER INTERNACIONAL, S.A., was not the marketing applicant before the regulatory agency; however there was an agency relationship between the patent owner and the marketing applicant during the regulatory review period. To show that the applicant is authorized to rely upon the activities of the marketing applicant before the Food and Drug Administration (FDA) the applicant has obtained a letter specifically authorizing such reliance (Exhibit 5).

For convenience, the information contained in this application will be presented in a format and order, which follows the requirements of 37 C.F.R. §1.740.

(1) The approved product ERTACZO™ (sertaconazole nitrate) Cream, 2%, contains the imidazole antifungal, **sertaconazole nitrate**. Sertaconazole nitrate contains one asymmetric carbon atom and exists as a racemic mixture of R and S enantiomers.

Sertaconazole nitrate is designed chemically as **(+/-)-1-[2,4-dichloro-beta-[(7-chloroenzo[b]thien-3-yl)methoxylphenethyl]imidazole nitrate**. It has a molecular

weight of 500.8. The molecular formula is $C_{20}H_{15}C_{13}N_2OS \cdot HNO_3$, and the structural formula is as follows:



(I)

(2) The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, §505(b).

(3) The approved product ERTACZO™ received permission for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, §505(b) by virtue of a letter sent by the Food & Drug Administration (FDA) dated December 10, 2003.

(4) The only active ingredient in ERTACZO™ (sertaconazole nitrate) Cream, 2%, is the imidazole antifungal, sertaconazole nitrate, which has not been previously approved for commercial marketing under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, prior to approval of NDA 21-385 by the FDA on December 10, 2003.

(5) This application for extension of patent term under 35 U.S.C. §156 is being submitted within the 60 day period pursuant

to 37 C.F.R. §1.720(f), which period will expire on February 6, 2004.

(6) The complete identification of the patent for which extension is being sought is as follows:

Inventors: Rafael Foguet, Marcial Moreno, Manuel Raga, Rosa M. Cuberes, Jose M. Castello, and Jose A. Ortiz

Patent No.: 5,135,943

Issue Date: August 4, 1992

Expiration Date: August 4, 2009 (17 years from issue)

(7) A true copy of the patent is attached hereto as Exhibit 3.

(8) No Terminal Disclaimer or Reexamination Certificate has been issued.

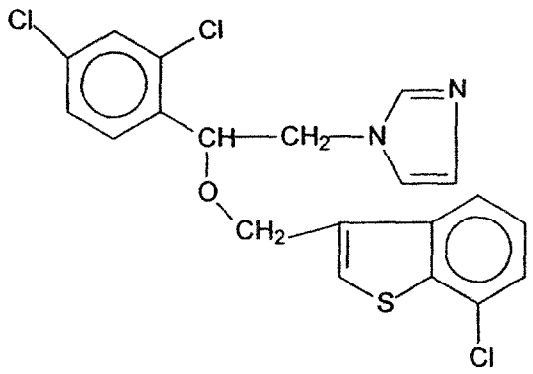
No Certificate of Correction has been filed. However, a petition to correct the inventorship of the Patent was filed on June 16, 2003. More specifically, Applicants requested that Rafael Foguet be removed as an inventor. A copy of the papers relating to the Petition to correct inventorship are attached hereto as Exhibit 2.

Enclosed are copies of the statements from the USPTO verifying payment of the maintenance fees 3.5 years after grant, 7.5 years after grant 11.5 years after grant (see Exhibit 4).

(9) U.S. Patent 5,135,943 claims the active compound of the approved product ERTACZO™ (sertaconazole nitrate) Cream, 2%

[see claim 1]; a pharmaceutical composition comprising the compound [see claims 2-5, 13 and 14]; methods of treating infection by administering the compound [see claims 6 and 8]; and a nitrate salt of the compound [see claim 12]. Claims 1-6, 8 and 12-14 are as follows:

1. A 1H-imidazole derivative compound of formula I:



(I)

or a nontoxic addition salt thereof.

2. A pharmaceutical composition for treating infections caused by fungi or yeasts in humans and pets, comprising said compound of claim 1 in an effective amount and in combination with a pharmaceutically acceptable carrier.

3. A pharmaceutical composition according to claim 2, in dosage unit form including 100 to 800 mg of said compound.

4. A pharmaceutical composition according to claim 3 for topical application, wherein said compound is present in a concentration from 0.1 to 5 %.

5. A pharmaceutical composition composed of 0.1 to 5 % by weight of said compound of claim 1 in a pharmaceutically acceptable carrier, said compound being present in an amount of from 100 to 800 mg.

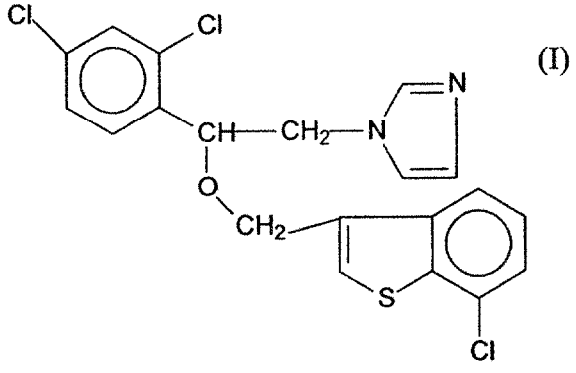
6. Method of treating infection caused by fungi or yeast in humans and pet animals, comprising

administering an effective amount of the composition according to claim 2.

8. Method of claim 6, wherein said administering comprises oral, injection, rectal, vaginal or topical route administering.

12. Compound according to claim 1, wherein said acid addition salt is a nitrate salt.

13. A pharmaceutical composition for treating fungal and yeast infections in humans and pets, comprising 100 to 800 mg of a member selected from the group consisting of a 1H-imidazole derivative compound of formula I:

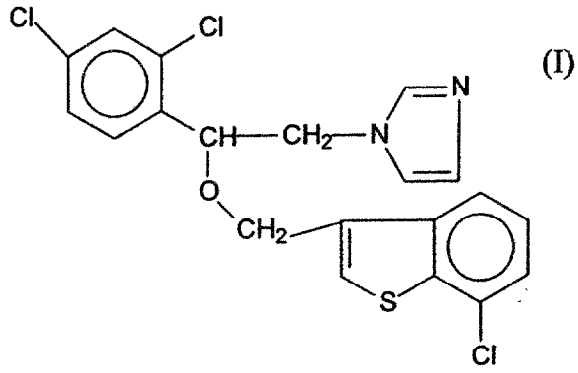


(I)

and nontoxic addition salts thereof in a pharmaceutically acceptable carrier.

14. A pharmaceutical composition according to claim 13, wherein said nontoxic addition salts include a mononitrate addition salt of said 1H-imidazole derivative compound.

The above-mentioned patent claims (e.g. claims 1-5 and 12-14) read on the active compound of the approved product ERTACZO™ (sertaconazole nitrate) Cream, 2%, which contains the imidazole antifungal, sertaconazole nitrate having the formula:



(I)

as well as a method of using the approved product as recited in claims 6 and 8, which utilizes the compound of the formula shown above.

(10) Relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review are as follows:

(A) An Investigational New Drug application (IND 50,726) for ERTACZO™ (sertaconazole nitrate) Cream, 2% was filed on May 31, 1996 and became effective on June 11, 1996.

(B) A New Drug Application (NDA 21-385) for ERTACZO™ (sertaconazole nitrate) Cream, 2% was filed under §505(b) of the Federal Food Drug & Cosmetic Act on September 28, 2001 and received by the FDA on September 28, 2001.

(C) The New Drug Application (NDA 21-385) for ERTACZO™ (sertaconazole nitrate) Cream, 2% was approved on December 10, 2003.

(11) As a brief description of the activities undertaken by applicant or applicants' representatives during the applicable regulatory review period, attached hereto is a chronology of the major communications between the applicant and the FDA from May 31, 1996 (the date of filing IND 50,726) to December 10, 2003 (the approval date of NDA 21-385)(Exhibit 6).

(12)(i) Applicant is of the opinion that U.S. Patent 5,135,943 is eligible for an extension under 35 U.S.C. §156 because it satisfies all requirements for extension as follows:

(a) 35 U.S.C. §156(a) - U.S. Patent 5,135,943 claims as a new compound the active ingredient in ERTACZO™ (sertaconazole nitrate) Cream, 2%, a pharmaceutical composition containing the compound and a method of treatment using the compound.

(b) 35 U.S.C. §156(a)(1) - U.S. Patent 5,135,943 has not expired before submission of this application.

(c) 35 U.S.C. §156(a)(2) - The term of U.S. Patent 5,135,943 has never been extended under 35 U.S.C. §156(e)(1).

(d) 35 U.S.C. §156(a)(3) - The application for extension is submitted by the owner of record of the patent in accordance with the requirements of paragraphs (1) through (4) of 35 U.S.C. §156(d) and the rules of the U.S. Patent & Trademark Office.

(e) 35 U.S.C. §156(a)(4) - The product ERTACZO™ (sertaconazole nitrate) Cream, 2%, has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. §156(a)(5)(A) - The commercial marketing or use of the product ERTACZO™ (sertaconazole nitrate) Cream, 2%, after the regulatory review period is the first permitted commercial marketing or use under the provision of the Federal Food, Drug and Cosmetic Act (i.e. Section 512) under which such regulatory review period occurred.

(g) 35 U.S.C. §156(c)(4) - No other patent has been extended for the same regulatory review period for the product ERTACZO™ (sertaconazole nitrate) Cream, 2%.

(12)(ii) The length of the extension of patent term of U.S. Patent 5,135,943 claimed by Applicant is 1776 days or 4.86 years. The length of the extension was determined pursuant to 37 C.F.R. §1.778 as follows:

(a) The regulatory review period under 35 U.S.C. §156(g)(4)(B) began on May 31, 1996 and ended December 10, 2003, which is a total of 2749 days or 7.53 years, which is the sum of (1) and (2) below:

(1) The period of review under 35 U.S.C. §156(g)(4)(B)(i), the "Testing Period", began on May 31, 1996 and ended on September 28, 2001, which is 1946 days or 5.3 years.

(2) The period of review under 35 U.S.C. §156(g)(4)(B)(ii), the "Approval Period", began on September 28, 2001 and ended on December 10, 2003, which is 803 days or 2.2 years.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph (12)(ii)(a) above (2749 days) less:

(1) The number of days in the regulatory review period which were on or before the date on

which the patent issued (August 4, 1992), which is (0) days; and

(2) The number of days during which applicant did not act with due diligence, which is (0) days; and

(3) One-half the number of days determined in subparagraph (12)(ii)(a)(1) after the patent issued (one-half of 1946) days, which is 973 days;

(c) The number of days as determined in subparagraph (12)(ii)(b) (1776 days of 4.86 years) when added to the original term of the patent (original expiration date - August 4, 2009) would result in the date June 15, 2014;

(d) Fourteen (14) years when added to the date of NDA approval of December 10, 2003 would result in the date of December 10, 2017;

(e) The earlier date as determined in subparagraphs(12)(ii)(c) and (12)(ii)(d) is June 15, 2014.

(f) Since U.S. Patent 5,135,943 issued after September 24, 1984, the period of extension may not exceed five (5) years. Five (5) years when added to the original expiration date of the

patent (August 4, 2009) would result in August 5, 2014.

(g) The earlier date as determined by subparagraph (12)(ii)(e) and (12)(ii)(f) is June 15, 2014.

(h) The limitations of 35 U.S.C. 156(g)(6) do not operate to further reduce the period of extension determined above.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

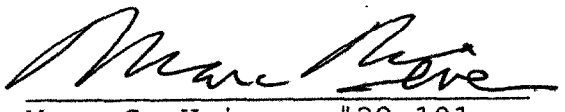
(14) The prescribed fee under 37 C.F.R. §1.20(j) for receiving and acting upon this application is attached as a check in the amount of $1,120.00. The Commissioner is authorized to charge any additional fees required by this application to Deposit Account No. 02-2448.

(15) All correspondence and inquiries may be directed to the undersigned, whose address, telephone number and fax number are as follows:

Marc S. Weiner
BIRCH, STEWART, KOLASCH & BIRCH, LLP
P.O. Box 747
Falls Church, VA 22040-0747
Phone: 703-205-8000
Fax: 703-205-8050

The present document is being submitted as one original and four copies are required under 37 C.F.R.§1.740(b) (5 copies total) and requested under M.P.E.P.§2753 (5 copies total).

Respectfully submitted

By: 

Marc S. Weiner, #32,181

MaryAnne Armstrong, PhD #40,069

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

MSW/sh
2294-0116M

Attachments: Exhibits 1-6

Exhibit 1

PATENT
2294-0116M

IN THE U.S. PATENT AND TRADEMARK OFFICE

Patent No.: 5,135,943

Issued: August 4, 1992

Assignee: Ferrer Internacional S.A.

For: 1H-IMIDAZOLE DERIVATIVE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME

POWER OF ATTORNEY AND APPOINTMENT OF AGENT PURSUANT TO 37 CFR 1.730

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Assignee, Ferrer Internacional S.A. a corporation organized and existing under the laws of Spain, represents that it is the Assignee of the entire right, title, and interest in and to United States Letters Patent 5,135,943 as evidence by the Assignment recorded with the USPTO on February 1, 1991 at Reel/Frame 005625/0795; and hereby appoints the practitioners at customer No. 002292 (Birch, Stewart, Kolasch & Birch, LLP) as its attorneys pursuant to 37 CFR 1.730 to conduct all business before the United States Patent and Trademark Office relative to an Application for Patent Term Extension pursuant to 35 USC 156 for the above-identified United States Letters Patent.

Please send all future correspondence concerning the above matter to Birch, Stewart, Kolasch & Birch, LLP or customer no. 002292, at the following address:

Post Office Box 747
Falls Church, Virginia 22040-0747
Telephone: 703/205-8000
Facsimile: 703/205-8050

Dated: February 2, 2004

Jorge Ramentol,
Director General
FERRER INTERNACTIONAL S.A.

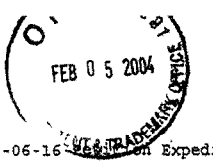


Exhibit 2

IN THE U. S. PATENT AND TRADEMARK OFFICE

Patent No.: 5,135,943 Docket No.: 2294-0114M
Issue Date: August 4, 1992
Assignee: Ferrer Internacional S.A.
For: 1H-imidazole derivative compounds and pharmaceutical compositions containing the same

PETITION TO EXPEDITE UNDER 37 CFR 1.182 THE PETITION TO CORRECT INVENTORSHIP UNDER 35 USC 256

Commissioner for Patents
P. O. 1450
Alexandria, VA 22313-1450

June 16, 2003

Sir:

The Commissioner is respectfully requested to expedite the decision requested in the following documents filed concurrently herewith namely:

(a) "PETITION TO CORRECT INVENTORSHIP UNDER 35 USC 256";

(b) "STATEMENT FROM CURRENT NAMED INVENTORS UNDER 37 CFR 1.324(b)(2)"; and

(c) "STATEMENT FROM ASSIGNEE UNDER 37 CFR 1.324(b)(3)"

Facts

It has recently been determined that the inventorship in the above-identified patent is incorrect. Such incorrect inventorship may adversely affect the validity of the above-identified patent. Ferrer Internacional S.A.,

the assignee of the entire right, title, and interest in the above-identified patent, has recently entered into business negotiations with a third party. Successful conclusion of these business negotiations, which will be advantageous to the assignee, requires a patent having the correct inventorship. Upon information and belief, it now takes from three to four months for the Commissioner to decide such petitions to change inventorship. Failure to promptly receive from the Commissioner a decision regarding inventorship may result in irreparable harm to the assignee.

Relief Requested

The assignee, through the undersigned attorney, respectfully requests that this petition to expedite be granted and that a decision on the merits of the requested change of inventorship be promptly made and communicated to the undersigned attorney and to all attorneys of record in the above identified patent.

Fees

A check in the amount of ONE-HUNDRED-THIRTY and xx/100 DOLLARS ($130.00) to cover the statutory fee required by 37 CFR 1.182 and 37 CFR 1.17(h) is attached hereto. If this

check is deficient or if any other fees are required, the Commissioner is authorized and requested to charge such fees to Deposit Account No. 02-2448.

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Marc S. Weiner, #32,181

MSW/DRM/jeb
2294-0114M

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

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IN THE U. S. PATENT AND TRADEMARK OFFICE

Patent No.: 5,135,943 Docket No.: 2294-0114M
Issue Date: August 4, 1992
Assignee: Ferrer Internacional S.A.
For: 1H-imidazole derivative compounds and pharmaceutical compositions containing the same

PETITION TO CORRECT INVENTORSHIP UNDER 35 USC 256

Commissioner for Patents
P. O. 1450
Alexandria, VA 22313-1450

June 16, 2003

Sir:

The Commissioner is respectfully requested to correct the inventorship in the above-identified patent pursuant to 35 USC 256; and 37 CFR 1.324.

In view of the documents entitled "STATEMENT FROM CURRENT NAMED INVENTORS UNDER 37 CFR 1.324(b)(2)" and "STATEMENT FROM ASSIGNEE UNDER 37 CFR 1.324(b)(3)" both filed concurrently herewith, the Commissioner is respectfully requested to remove Rafael Foguet as an inventor and issue a certificate pursuant to 37 CFR 1.234(a).

A check in the amount of ONE-HUNDRED-THIRTY and xx/100 DOLLARS ($130.00) to cover the statutory fee required by 37 CFR 1.234(b)(4) and 37 CFR 1.20(b) is attached hereto. If this check is deficient or if any other fees are required,

the Commissioner is authorized and requested to charge such fees to Deposit Account No. 02-2448.

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Marc S. Weiner, #32,181

MSW/DRM/jeb
2294-0114M

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

P:\2294\0114M\2003-06-05 Statement of Inventors.doc

IN THE U. S. PATENT AND TRADEMARK OFFICE

Patent No.: 5,135,943
Issue Date: August 4, 1992
Assignee: Ferrer Internacional S.A.
For: 1H-imidazole derivative compounds and pharmaceutical compositions containing the same

STATEMENT FROM CURRENT NAMED INVENTORS UNDER 37 CFR 1.324(b)(2)

We, the undersigned, declare that:

1. We are all the currently named inventors in the above-identified United States Patent.

2. We agree and request that the inventorship be changed by deleting Rafael Foguet as an inventor.

3. We hereby declare that all statements made herein of our own knowledge are true and that statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the Unites States Code and that such willful false statements may jeopardize the validity of the above-identified patent.

6-06-2003 — date — Rafael Foguet

10-06-2003 — date — Marcial Moreno

6-6-2003 — date — Manuel Raga

6-06-2003 — date — Rose M. Cuberes

6-06-2003 — date — Jose M. Castello

6-6-2003 — date — Jose A. Ortiz

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IN THE U. S. PATENT AND TRADEMARK OFFICE

Patent No.: 5,135,943 Docket No.: 2294-0114M
Issue Date: August 4, 1992
Assignee: Ferrer Internacional S.A.
For: 1H-imidazole derivative compounds and pharmaceutical compositions containing the same

STATEMENT FROM ASSIGNEE UNDER 37 CFR 1.324(b)(3)

The undersigned declares that:

1. I am the General Manager of Ferrer Internacional S.A. hereafter referred to as "ASSIGNEE", and have authority to act in this matter on behalf of the ASSIGNEE.

2. The ASSIGNEE is the owner of the entire right, title and interest in the above-identified United States patent by virtue of an assignment duly executed and duly recorded amongst the records of the United States Patent and Trademark Office.

3. The ASSIGNEE agrees and requests that the inventorship be changed by deleting Rafael Foguet as an inventor.

4. I hereby declare that all statements made herein of my own knowledge are true and that statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under section 1001 of Title 18 of the Unites States Code and that such willful false statements may jeopardize the validity of the above-identified patent.

10-06-03
date

Jorge Ramentol
General Manager
Ferrer Internacional S.A.

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IN THE U. S. PATENT AND TRADEMARK OFFICE

Patent No.: 5,135,943 Docket No.: 2294-0114M
Issue Date: August 4, 1992
Assignee: Ferrer Internacional S.A.
For: 1H-imidazole derivative compounds and pharmaceutical compositions containing the same

REVOCATION OF POWER OF ATTORNEY, SUBSTITUTE POWER OF ATTORNEY, AND CHANGE IN CORRESPONDENCE ADDRESS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The Assignee of record of the entire right, title and interest in the above-identified patent hereby revokes any and all previous powers of attorney, and hereby appoints **the practitioners at CUSTOMER NO. 002292 (BIRCH, STEWART, KOLASCH & BIRCH, LLP)** as the attorneys of the Assignee to receive all correspondence relating to the above-identified application or patent and to transact all business in the United States Patent and Trademark Office connected therewith, with full power of substitution and revocation, and the Assignee ratifies any act done by the Assignee's attorneys in respect of this patent. The new correspondence address is:

BIRCH, STEWART, KOLASCH & BIRCH, LLP or Customer No. 002292
P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

The undersigned (whose title is supplied below) is empowered to sign this Revocation and Substitute Power of Attorney on behalf of the Assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

10-25-03
date

Jorge Ramentol
General Manager
Ferrer Internacional S.A.

Exhibit 3

US005135943A

United States Patent [19]

Foguet et al.

[11] Patent Number: 5,135,943

[45] Date of Patent: Aug. 4, 1992

[54] 1H-IMIDAZOLE DERIVATIVE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME

[75] Inventors: Rafael Foguet; Marcial Moreno; Manuel Raga; Rosa M. Cuberes; Jose M. Castello; Jose A. Ortiz, all of Barcelona, Spain

[73] Assignee: Ferrer Internacional S.A., Barcelona, Spain

[21] Appl. No.: 649,764

[22] Filed: Feb. 1, 1991

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 451,823, Dec. 15, 1989, abandoned, which is a continuation-in-part of Ser. No. 366,756, Jun. 14, 1989, abandoned, which is a continuation of Ser. No. 694,645, Jan. 24, 1985, abandoned.

[30] Foreign Application Priority Data

Feb. 2, 1984 [ES] Spain 529608
Jun. 1, 1984 [ES] Spain 533353
Aug. 6, 1984 [ES] Spain 535656

[51] Int. Cl.[5] A61K 31/415; A61K 31/38; C07D 403/12

[52] U.S. Cl. 514/397; 548/336

[58] Field of Search 548/336; 514/397

[56] References Cited

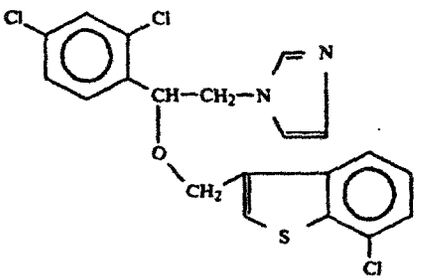
U.S. PATENT DOCUMENTS

4,272,545 6/1981 Walker 548/336
4,402,968 9/1983 Martin 548/336
4,410,539 10/1983 Cross et al. 548/336
4,463,011 7/1984 Ogata et al. 548/336
4,496,572 1/1985 Cross et al. 548/336
4,500,536 2/1985 Yoshida et al. 548/336

Primary Examiner—Johann Richter
Attorney, Agent, or Firm—Michael J. Striker

[57] ABSTRACT

The 1H-imidazole derivative compound of formula I:



(I)

and its nontoxic addition salts, particularly the nitrate addition salt, are more effective as antimycotic agents and are unexpectedly safer than the corresponding prior art compounds, especially the compound in which the sulfur atom of the benzothiophene ring of the above compound is replaced by an oxygen atom. Pharmaceutical compositions containing an effective amount of the compound of formula I, e.g. 1 to 5% by weight, in a pharmaceutical carrier are safer, more effective, and, in some cases, more reliable with fewer side effects than currently used antimycotic preparations.

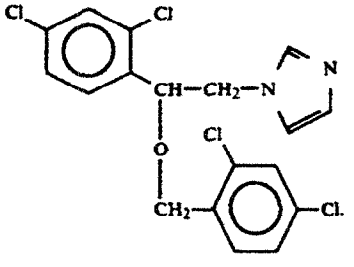
14 Claims, No Drawings

1H-IMIDAZOLE DERIVATIVE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAMEBACKGROUND OF THE INVENTION

This application is a continuation-in-part of application Ser. No. 451,823, filed Dec. 15, 1989, which is, in turn, a continuation-in-part application of Ser. No. 366,756, filed Jun. 14, 1989 and abandoned Apr. 5, 1990; which is a continuation of application Ser. No. 694,645, filed Jan. 24, 1985 and abandoned Jul. 27, 1989.

This invention relates to antimycotic pharmaceutical compositions and, more particularly, to 1H-imidazole derivative compounds and pharmaceutical compositions containing those compounds, especially antimycotic pharmaceutical compositions, i.e. pharmaceutical compositions for the treatment of infections in humans and animals, which are due to infection by fungi and yeast microorganisms. The invention also relates to fungicidal compositions for application to crops to destroy fungi and other microorganisms.

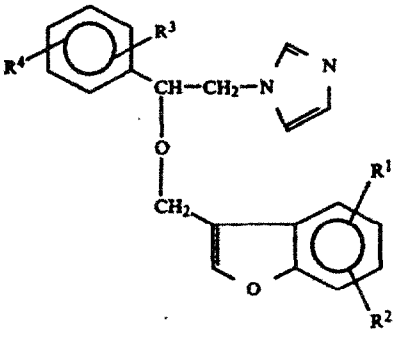
A number of compounds with antimycotic and/or fungicidal properties, which are useful in pharmaceutical compositions, are currently known. These include the commercially successful Miconazole having the formula II



(II)

Miconazole has a structure chemically similar to the 1H-imidazole derivative compounds of the invention. Miconazole is effective against a number of yeasts, dermatophytes and fungi. This effectiveness can be measured by culturing these microorganisms in vitro and applying a preparation containing the antimycotic compound, Miconazole. The results of this type of *in vitro* experiment is expressed in terms of the Minimum Inhibitory Concentration (MIC), i.e. the minimum concentration which inhibits the growth of the microorganism. For example, the MIC for Miconazole against a particular *Candida albicans* strain is found to be 10.7 micrograms/milliliter. The effectiveness of Miconazole as an antimycotic compound is measured in vivo by applying a suspension containing the drug to the skin of a number of animals and measuring the proportion of animals on which growth of the microorganism is inhibited as a function of time. Typically, after 25 days, about ½ of the animals were cured, when treated with a cream containing 2 % by weight Miconazole. Of course, any pharmaceutical preparation for treating a disease in a human must satisfy certain toxicity requirements. Therefore, toxicity tests are required to show that the preparation may be administered safely. Toxicity tests have been performed on the 1H-imidazole derivative compounds of the invention and on Miconazole and other known compounds having antimycotic properties. In toxicity tests the LD_{50} (the dose at which 50 % mortality occurs) is measured. For Miconazole, for example, the LD_{50} in mouse is about 2500 mg/kg for oral administration, 600 mg/kg for intraperitoneal administration and over 5000 mg/kg for subcutaneous administration.

Other compounds having a structure similar to applicants' compound include those described in U.S. Pat. No. 4,402,968, issued to Martin, Sep. 6, 1983. These compounds are also imidazole derivative compounds and have the following general formula III as claimed in the Martin Patent:



(III)

wherein R^1, R^2, R^3 and R^4 may be a hydrogen atom or a halogen atom, especially a chlorine atom. The in vitro fungicidal activity of one compound of formula III, in which all the R groups are chlorine radicals, was reported in the patent against several fungi. Measured in vitro against *Candida albicans* this compound has a MIC of about 10 micrograms per milliliter. A method of measurement of in vivo fungicidal activity was also described. However, as will be seen from the results described below, these compounds are comparatively toxic.

Other compounds having antimycotic properties are described in U.S. Pat. No. 4,272,545, issued to Walker. However, these antimycotic compounds have a structure which is considerably different from the structure of either the applicants or those of the Martin Patent. They have also been tested in vivo and in vitro and found effective against a large variety of fungi and yeast.

The current prior art antimycotic compounds, which are closest in structure to the applicants' compound, namely those of the Martin Patent, have an unexpectedly undesirably high toxicity, as measured in a variety of ways in comparison to the compounds described herein. Furthermore, the compounds of the present invention are more effective as in vitro fungicidal agents.

Other toxicological properties of the antimycotic compounds described in the Martin Patent are also poor. These poor toxicological properties imply that it is comparatively more dangerous to expose a human or pet to the compounds of the Martin Patent than to the compounds of the invention. The data, which will be presented below, also imply that 1H-imidazole derivative compounds of the invention can be applied in larger amounts, but as safely, as a correspondingly smaller concentration of the compounds of the Martin patent.

SUMMARY OF THE INVENTION

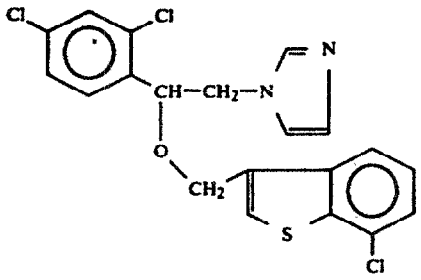
It is an object of the present invention to provide new 1H-imidazole derivative compounds having improved antimycotic and/or antifungicidal activity, but which

are also unexpectedly safer, in comparison to the comparable prior art compounds.

It is another object of the present invention to provide new antimycotic IH-imidazole derivative compounds, which are more effective, are safer to use on humans and pets and also in larger amounts than the current comparable prior art compounds and which are more reliable and faster acting for some microorganism infections.

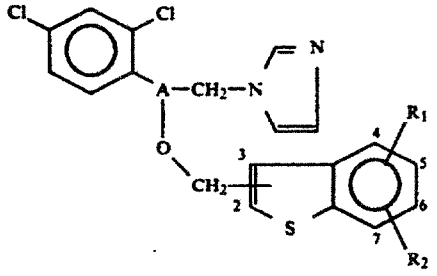
According to the invention, the 1H-imidazole derivative compounds having the above-mentioned improved pharmaceutical properties, including improved antimycotic activity and toxicological properties, comprise 1-[2-(7-chloro-3-benzo[b]thienyl)methoxy]-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole, and nontoxic addition salts thereof, preferably the mononitrate and the heminaphthanlene-1,5-disulphonate.

The novel 1H-imidazole derivative compound of the invention also has the following general formula I:



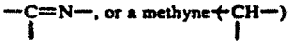
(I)

A number of other new 1H-imidazole derivative compounds of the following general formula I' have also been prepared and tested:



(I')

wherein A is an imino- ,



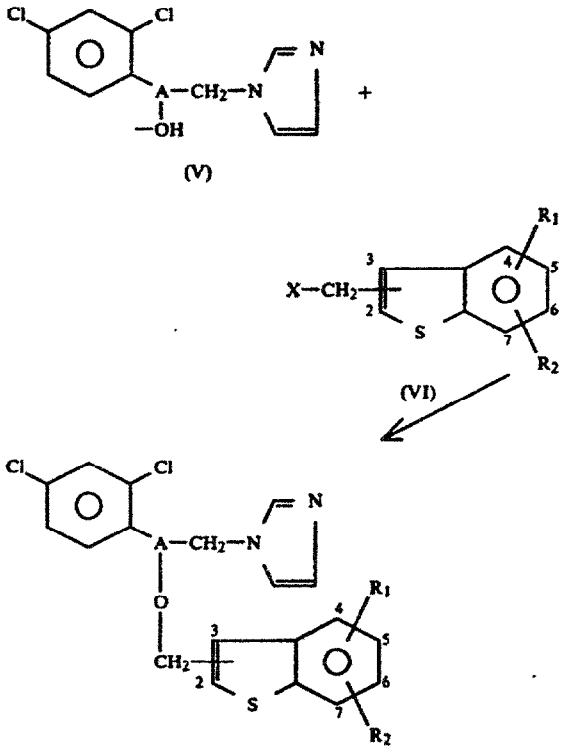
group, R_1 and R_2 are independently hydrogen or halogen selected from chlorine, bromine or fluorine in any of the 2, 4, 5, 6 or 7 positions of the benzo[b]thiophene group, and the methylene -CH_2-group is bonded to the benzo[b]thiophene group in its 2 or 3 position. These compounds also show antimycotic properties.

The antimycotic compound of the invention, the compound of formula I, will be hence forth referred to as Sertaconazole, for convenience. Pharmaceutical preparations with antimycotic properties are described hereinbelow.

The compound of formula I had a melting point of 146–7° C. The corresponding nitrate addition salt had a melting point of 156–7° C. Mass spectra and elemental analysis also confirmed the structure of the compound of formula I. See Manuel Raga, Celia Palacin, Josep Ma. Castello and Jose Ortiz and Ma. Cuberes and Marcial Moreno-Manas, Eur. J.Med. Chem. 21, pp 329–332(1986).

PREPARATION OF THE DERIVATIVE COMPOUNDS

The compounds of the present invention may be prepared according to the following scheme:



In the starting compounds of the formula V, A has the same meaning as stated above, and in the starting compounds of the formula VI, X is chlorine or bromine, R_1 and R_2 have the same meaning stated above and likewise, the methylene group (—CH_2—) is bonded to the benzo[b]thiophene group in the same position as defined above. A similar process is used to prepare the compounds described in the Martin reference referred to in the Background Section.

The reaction between the oxime or the alcohol of the formula V and the halides of the formula VI occurs conveniently in the presence of a suitable mineral base strong enough to ionize the compounds of the formula V such as hydroxides, or alkaline or alkaline-earth hydrides, with potassium hydroxide and sodium hydride, preferably employed.

The reaction is advantageously performed within a wide temperature range (from −55° C. to 100° C.) and in an aprotic solvent selected from an alkanone with up to 6 carbon atoms or a polyalkylated amide, with acetone or hexamethylphosphorotriamide preferably employed.

After purification, the acid addition salts may be obtained by treating with respective acids in a medium composed of an organic solvent. The organic solvent is an alcohol with 1 to 4 carbons, preferably ethanol or n-butanol, or may be a ketone such as acetone. A sol-

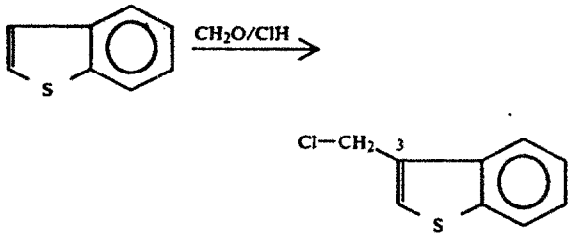
vent which is a mixture of an organic solvent and water may also be used.

The described reaction steps lead to the compounds of the formula I according to the present invention.

The oxime and alcohol used as starting material of the formula V are already known and are obtained according to the processes described by Von. G. Mixich and K. Thiele (Arzneimittel-Forschung, 29(II), Nr.10, 1510-3, 1979)—oxime, .Z configuration—and by E.F. Godefroi, et al (J. Med. Chem., 12, 784–9, 1969)—Alcohol, for example by treating 1-(2,4-dichlorophenyl)-2-(1H-imidazol-1-yl) ethanone with hydroxylamine or sodium borohydride, respectively.

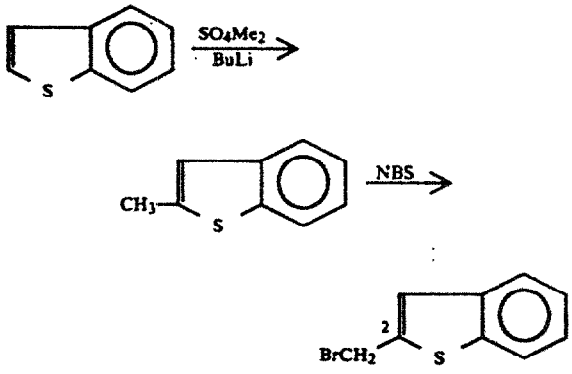
The halides of the formula VI are obtained by the known methods of organic chemistry, e.g.:

a) from benzo[b]thiophene either by chloromethylation (R. Neidlen and E.P. Mrugowski: Arch. Pharm. [Weinheim, Ger.,] 308(7), 513–9, 1975):



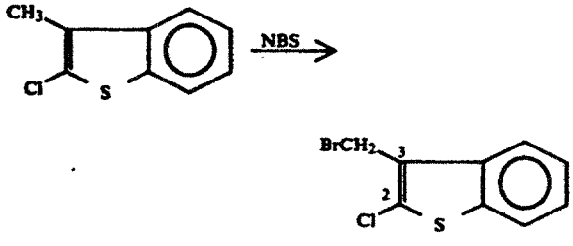
(VI, X = Cl, R_1 = R_2 = H, 3 position)

or by methylation and final bromination (D.A. Shirley and M.D. Cameron: JACS, 74, 664, 1952; U.S. Pat. No. 4,282,227):



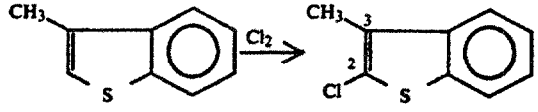
(VI, X = Br, R_1 = R_2 = H, 2 position)

b) from 2- chloro-3-methylbenzo[b]thiophene by bromination (European Pat. No. 54,233):



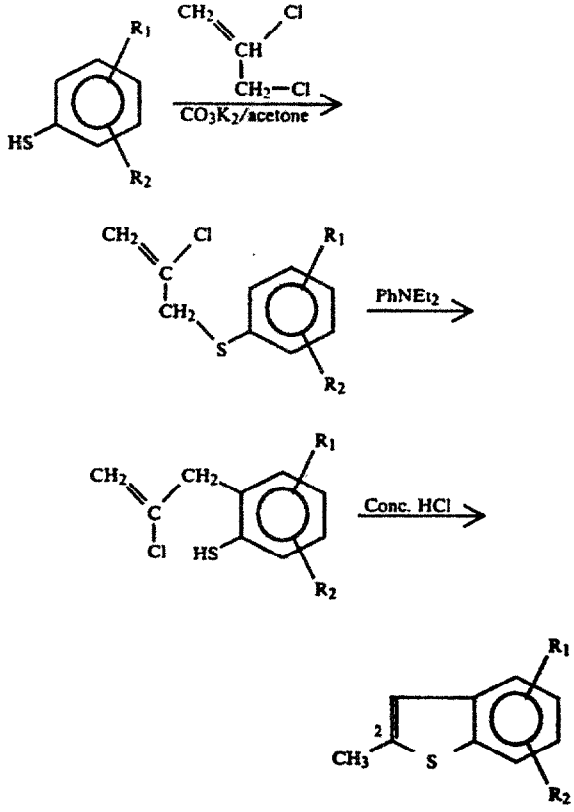
(VI, X = Br, R_1 = 2-Cl, R_2 = H, 3 position)

and 2- chloro-3-methylbenzo[b]thiophene is in turn obtained by chlorination of 3- methylbenzo[b]thiophene (V.I. Dronov et al, CA, 79, 115388f):



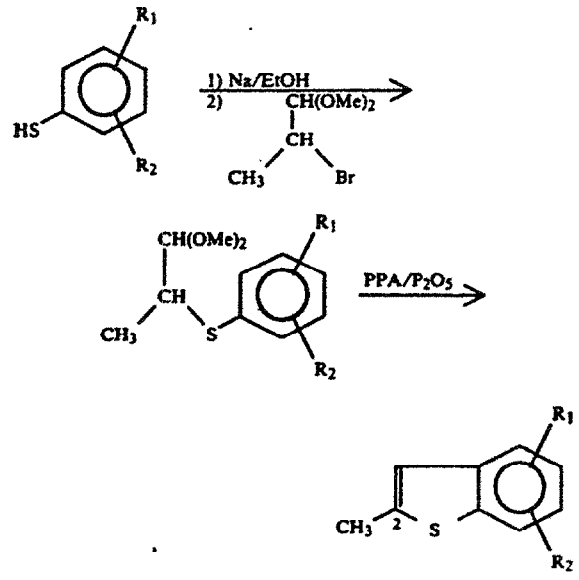
(VI, X = H, R_1 = 2-Cl, R_2 = H, 3 position)

c) from the corresponding thiophenol by total synthesis, for example, 2- chloro-2-propenyl-phenylthioether is formed by treating 2,3- dichloropropene, transposition in N,N-diethylaniline and cyclization with concentrated hydrochloric acid (W.K. Anderson and E.J. LaVoie, J. Chem. Soc., Chem. Commun., (5), 174, 1974; W.K. Anderson et al, J. Chem. Soc., Perkin Trans. 1, (1), 1–4, 1975):



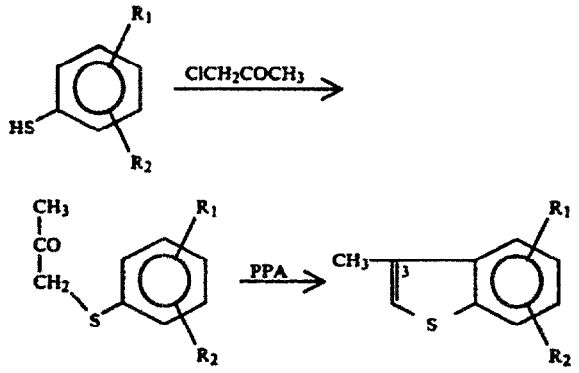
(VI, X = H, 2 position)

or by an alternative process also from the corresponding thiophenol by total synthesis, for example by forming respective 2- phenylthiopropionaldehyde acetal by treatment with 2-bromopropionaldehyde in sodium ethoxide and cyclization with an admixture of polyphosphoric acid and phosphorous pentoxide (Yasuo Matsuki and Fusaji Shoji, Nippon Kagaku Zasshi, 86,(10), 1067–72. 1965):



(VI, X = H, 2 position)

d) in a similar manner the 3-position compounds are also obtained from the corresponding thiophenol by total synthesis and forming respective phenylthioacetone by treatment with chloroacetone and cyclization with polyphosphoric acid (N.B. Chapman, et al, J. Chem. Soc. C., (5), pp. 512-22, 1968; N.B. Chapman, et al, ibid, (5), 2747-51, 1968):



(VI, X = H, 3 position)
PPA: Polyphosphoric acid
NBS: N-bromosuccinimide

Halogenation of intermediates (VI, X=H) with N-bromosuccinimide or with N-chlorosuccinimide in carbon tetrachloride, under the conditions described by N.B. Chapman, et al; J. Chem. Soc. C., (5), 512-22, 1968) and N.B. Chapman, et al (ibid., (5), 2747-51, 1968), leads to the intermediates (VI, X=Br or Cl).

The starting thiophenol, when R_1 or R_2 are halogen in metaposition, leads to correspondingly substituted 4- or 6- position benzo[b]thiophenes, enabling the isomers to be separated by customary methods of organic chemistry. Column chromatography is a preferred method of separation.

COMPARATIVE STUDY OF PHARMACOLOGICAL PROPERTIES

Comparative in vitro and in vivo antimycotic activities of the compound of formula I, Sertaconazole, versus Miconazole and the compounds of the Martin patent, which have the closest structure to Sertaconazole, are reported hereinbelow. Clinical data are also included. The data show that Sertaconazole has a higher antimycotic activity than these prior art compounds. Furthermore, toxicological data for these compounds also shows that Sertaconazole is surprisingly and unexpectedly safer to administer to humans and pets in a method of treating an infection due to fungi or yeast.

The compounds of the Martin patent, which are the closest in structure to Sertaconazole, also have an unexpectedly large toxicity and are much less safe than Miconazole. In view of this finding, it is not surprising that Miconazole is the more frequently used compound commercially. As a result, comparison has been made with Miconazole as well as with the compounds described in the Martin patent.

1. In vitro Fungicidal Activity Measurements

Minimum Inhibitory Concentrations (MICS) of Sertaconazole and Miconazole against 107 yeasts, 47 dermatophytes and 4 fungi were determined by a two-fold dilution method. The results of these measurements are shown in the following Table I.

These results show that Sertaconazole has a somewhat different, but similar, spectrum of in vitro activity in comparison to Miconazole. Particularly, Sertaconazole is more active against *Candida albicans* (43.9 % higher), *Candida s.p.* (47.4% higher) and *Scopulariopsis* (75 % higher). Thus Sertaconazole is more effective than the most common commercially used product in the case of several microorganisms.

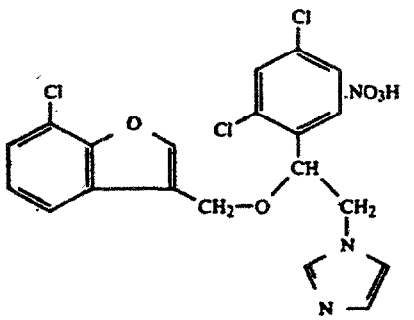
Minimum Inhibitory Concentrations (MICS) of Sertaconazole were also measured in comparison to four of the compounds described in the Martin Patent, including a compound, referred to herein as Martin Compound 1, which has the same structure as Sertaconazole, expect that the sulfur in the benzothiophene ring is replaced by an oxygen.

TABLE I

Minimum Inhibitory Concentration of Sertaconazole and Miconazole against Different Microorganisms

Microorganism	# strains	Sertaconazole microgram/ml	Miconazole microgram/ml
Yeasts			
Candida albicans	52	6.0	10.7
Candida tropicalis	10	5.6	5.6
Torulopsis glabrata	10	1.5	1.1
Candida s.p.	15	0.5	0.95
Malasezzia furfur	20	25/8	19/2.8
Dermatophytes			
Trichophyton rubrus	10	0.4	0.3
Trichophyton mentagrophytes	30	2.6	2.8
Microsporum canis	4	2.8	2.0
Others	3	2.5	4.0
Fungi			
Scopulariopsis brevicaulis	4	8.0	32.0
Gram-positive germs	21	0.97	0.88

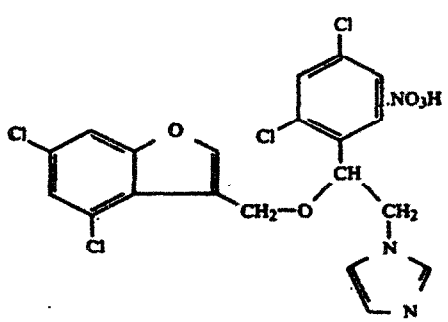
The structure of the Martin Compound 1 is as follows:



M1

The structure of Martin Compound 2 and 3 is the same as the Martin Compound 1 except that the chlorine substituent on the benzothiophene ring is in the 6 and the 5 position, respectively, instead of the 7 position. Furthermore, the methylene group (—CH_2—) is bonded to the benzo[b]furan group in the Martin Compound 3 in the 2 position instead of the 3 position.

The structure of the Martin Compound 4 is as follows:



M4

The results of comparative in vitro testing of Sertaconazole and these four Martin compounds are shown in the following Table II against 16 microorganisms.

The reading time is the time interval from the time of inoculation to the time of measurement.

Table II also shows the geometric mean of all measurements. Calculation of these geometric mean values shows that Sertaconazole is 24 % more effective than Martin Compound 1; 54 % more effective than Martin Compound 2; 16 % more effective than Martin Compound 3 and 54 % more effective than Martin Compound 4.

Thus, Sertaconazole shows an increased antimycotic activity in relation to all the Martin Compounds studied, including Martin Compound 1, in which only a benzothiophene ring sulfur is replaced by oxygen

Theoretical calculations of bond angles and electron densities made by the method of Del Re, et al. Biochem.Biophys.Acta, 75, 153–182(1963) have confirmed that significant differences in chemical properties can occur, because of replacement of the oxygen atom in the benzothiophene ring with the sulfur atom. For example,

TABLE II

	MIC values (μg/ml)										
Microorganism	SZ	M1		SZ	M2		SZ	M3		SZ	M4	
C. albicans 14	1	2	*a*	0.25	0.25	*d*	0.5	0.5	*d*	0.5	0.5	*d*
C. albicans 15	0.5	1	*a*	0.06	0.06	*d*	0.03	0.06	*d*	0.03	0.03	*d*
C. albicans 31	8	8	*b*	4	4	*e*	4	4	*e*	4	8	*e*
C. albicans 32	8	8	*b*	4	4	*e*	4	4	*e*	4	8	*e*
C. albicans ATCC E-10231	1	2	*a*	0.5	0.5	*d*	0.5	0.5	*d*	0.5	0.5	*d*
C. pseudotropicalis 21	0.03	0.03	*c*	0.03	0.06	*f*	0.03	0.03	*f*	0.03	0.03	*f*
C. krusei 24	1	1	*a*	0.25	0.05	*d*	0.125	0.125	*d*	0.125	0.5	*d*
C. krusei 24	0.25	0.25	*b*	0.25	0.5	*e*	0.25	0.25	*e*	0.25	0.5	*e*
C. parapsilosis 19	1	1	*c*	0.25	1	*f*	0.25	0.5	*f*	0.25	0.5	*f*
C. parapsilosis 19	0.5	0.5	*b*	0.25	1	*e*	0.5	1	*e*	0.5	0.5	*e*
C. stellatoidea 36232	1	1	*c*	0.25	0.5	*f*	0.5	0.5	*f*	0.5	0.5	*f*
C. stellatoidea 36232	0.25	0.5	*a*	0.06	0.06	*d*	0.06	0.125	*d*	0.06	0.06	*d*
C. stellatoidea 36232	4	4	*b*	1	1	*e*	0.5	4	*e*	0.5	0.5	*e*
C. guillermondii	0.5	0.5	*a*	0.25	0.5	*d*	0.25	0.25	*d*	0.25	0.5	*d*
C. guillermondii	0.25	0.5	*b*	0.25	0.5	*e*	0.125	0.25	*e*	0.125	0.5	*e*
C. tropicalis 25	8	8	*b*	8	8	*e*	4	8	*e*	4	8	*e*
Geometric means	0.876	1.09		0.366	0.565		0.336	0.497		0.336	0.518	
Increase of Sertaconazole activity	24%			54%			16%			54%		

SZ Sertaconazole
M1, M2, M3, M4 Martin compounds
[a] Casitone medium. Reading time 60 h
[b] YNB medium. Reading time 60 h
[c] Sabouraud medium. Reading time 60 h
[d] Casitone medium. Reading time 48 h
[e] YNB medium. Reading time 48 h
[f] Sabouraud medium Reading time 48 h

applicants have found by this theoretical method that the sulfur atom in Sertaconzole is significantly less negatively charged than the corresponding oxygen atom in Martin Compound 1. Furthermore, the theoretical results for the electron densities and the bond angles show that, relative to Martin Compound 1, Sertaconzaole has decreased polarity, increased lipophylicity, increased molecular volume, decreased gastrointestinal absorption and decreased toxicity.

2. In Vivo Activity

Dermal infection in albino female guinea pigs by Trichophyton mentagrophytes has been studied. Animals were distributed in three groups: a) a control group of infected untreated animals; b) a sertaconazole group of infected and treated animals; and c) a miconazole group of infected and treated animals. Animals were depleted and a 0.4 ml suspension of the microorganism was applied on the depleted area. Treatment with each of the test drugs was made by application of 1 g of 2% cream on the depleted area on the 4th, 5th and

6th day after infection. The results are shown in the following Table III:

TABLE III

Relationship of Negative Cultures to Total Cultures (% microbiological healing) at days 18, 25 and 32 Postinfection.

Treatment group	18 days	25 days	32 days
Control	0/24(0%)	0/24(0%)	5/24(21%)
Compound 25	27/48(56%)	36/48(75%)	40/48(84%)
Miconazole	3/48(6%)	13/48(28%)	21/48(44%)

Although in the in vitro experiment with *Trich. metagrophytes*, Sertaconazole was not much more active than Miconazole, in this in vivo experiment with the same microorganism Sertaconazole was surprisingly remarkably more active than Miconazole. 9 times higher on the 18th day, 2.7 times higher on the 25th day and 1.9 times higher on the 32nd day postinfection. These results show that although only small structural changes are involved large surprising changes in the rates of cure occur. These results are consistent with clinical trials.

Besides the above in vivo experiments vaginal infection by *Candida albicans* was studied in female mice. Standard methods were used. Seven days after infection sertaconazole was found to heal 75 % of the animals treated whereas miconazole only healed 12.5 %. Similar results were found in experiments where repeated dosages of active compound were used after infection. These in vivo results confirmed the surprising speed of action of Sertaconazole in comparison to the prior art compounds.

3. Toxicological Comparisons

Toxicity of Sertaconazole, Microazole and Martin's compounds 1, 2 and 3, as shown below, has been tested by standard methods. Both acute toxicity, subacute toxicity and chronic toxicity were studied

Oral, intraperitoneal and subcutaneous acute toxicity of sertaconazole and miconazole have been investigated. LD50 in mouse and rat, male and female, were measured. The results are shown in Table IV following:

TABLE IV

Lethal Dose(LD50) of Sertaconazole and Miconazole through Three Different Administration Routes in Males

Administration	Animal	Sertaconazole mg/kg	Miconazole mg/kg
Oral	mouse	>8000	2,560
Oral	rat	>8000	920
Intraperi-	mouse	>8000	662
toneal	rat	>8000	1,185
Subcutaneous	mouse	>8000	>5000
	rat	>8000	>5000

Table IV shows that Sertaconazole is an order of magnitude less toxic by oral and intraperitoneal routes than the prior art compound, Miconazole. Subcutaneous acute toxicity was also significantly less for Sertaconazole than Miconazole. This shows that a pharmaceutical preparation containing Sertaconazole is significantly safer to give to a person or pet suffering from an infection due to microorganisms than Miconazole (assuming equal amounts of the active ingredient are used, which is most likely since Sertaconazole is more effective than Miconazole).

In a study of prolonged subacute toxicity of Miconazole in rats, among other effects, significant hepatomegalias in females with a dosage of under 30 mg/kg p.o. and in males with a dosage of under 60 mg/kg p.o. were observed. In contrast, Sertaconazole did not show this effect, caused by hepatocite microsomal enzymes, up to a dosage of 300 mg/kg.

Chronic toxicity of Miconazole in rats resulted in a conclusion that 100 mg/kg or more dosage caused 32 % mortality, while no mortality was observed with Sertaconazole, even at dosage levels of 300 mg/kg.

Based on these finds a safe dosage for Miconazole is about 10 mg/kg, while a safe dosage for Sertaconzole is about 150 mg/kg, i.e about 15 times higher.

Similar toxicological experiments were performed for Sertaconazole, Sertaconazole nitrate, Martin Compounds 1, 2, 3 and 4. The results are shown in Table V hereinbelow. They show that Sertaconazole is unexpectedly and surprisingly less toxic than the Martin compounds.

Sertaconazole is 8 to 15 times less toxic than the Martin Compound 1, the compound of the prior art having a structure which is closest to that of Sertaconazole.

TABLE V

Compound	Toxicological Data LD_{50} (mg/kg) (Swiss mice i.p.)	LD_0 (mg/kg) (Swiss mice i.p.)
Sertaconazole base	8000	4000
Sertaconazole nitrate	8000	2000
Martin compound 1	518	285
Martin compound 2	640	235
Martin compound 3	640	423
Martin compound 4	<1000[a]	Not determined

[a]Approximate value.

Furthermore and in addition to the results shown in Table V, the mice given Martin Compounds 1 and 3 revealed evident signs of intoxication in the central nervous system, which possibly caused the death of most animals. Such signs included convulsions and Straub tail(vertical righting of the tail). These signs were not observed in mice given Sertaconazole at any dosage level. Post mortem examination showed that 80 % of the mice given Martin Compound 3 had generalized pulmonary edema and congestion to such an extent that alone could have caused their death.

Thus, Sertaconzole is unexpectedly and surprisingly safer than the closest prior art, Martin Compound 1 This implies that a higher concentration of Sertaconazole can be used safely in a pharmaceutical preparation to treat an infection in humans and pets than Martin Compound 1. However, since Sertaconazole is also more effective as an in vitro fungicidal agent, it is not necessary to use a higher concentration.

In conclusion, Sertaconazole has been shown to be unexpectedly and surprisingly better as an antimycotic agent than the closest prior art compounds.

4. Clinical Evaluation of Pharmaceutical Preparations for Treating Infections in Humans

Human clinical trials were performed with Sertaconazole nitrate and Miconazole nitrate acid addition salts. Randomized double blind trials were carried out with 502 patients suffering from cutaneous mycosis as confirmed by microscopic examination and microbiological culture. 247 patients were treated with 2 % Sertaconazole cream and the remaining 255 patients were treated with 2 % Miconazole cream. All patients received scheduled treatment for 28 days and were followed up for an additional 28 days for possible re-

lapses. The most important conclusions from these clinical trials were that Sertaconazole was 20.8% more effective than Miconazole. Also it was 100 % effective against *Trichophyton rubrum*, which produces a particularly stubborn infection, as compared to 79 % for Miconazole. Furthermore, there were 5 cases of contact dermatitis in the experiments with Miconazole, while Sertaconazole showed no such side effects.

Sertaconazole generally shows an antibacterial and antiprotozoal activity as well as an antimycotic behavior.

PHARMACEUTICAL COMPOSITIONS

For their pharmaceutical, veterinary and clinical use the compounds of the present invention or their pharmaceutically acceptable acid addition salts can be administered, in solid, semi-solid or liquid form in tablets, coated tablets, capsules, powders, suppositories, liquid solutions, suspensions, creams, lotions, ointments and the like, together with pharmaceutically acceptable non-toxic carriers or excipients normally employed. They can also be administered by the in3ectable route, rectal route and by vaginal-intrauterine route in the form of ovulum, vaginal tablets, ointment, cream, pessary, lotion, etc. They can be administered by the topical route in the form of cream, lotion, ointment, emulsion, solution shampoo, powder, gel and so forth.

Topical application is the preferred method of administration in clinical usage. Topical pharmaceutical compositions containing the compounds of the present invention exhibit antiyeast, antifungal, antiprotozoal and antibacterial activity over a wide range of concentrations, for example, from about 0.1 % to 15 % by weight of the composition, to be applied on the infected skin or mucosa, preferably in 2 to 3 daily applications.

For systematic (oral or parenteral) or rectal administration, it is expedient to administer the active ingredient in amounts between 1 and 50 mg/kg body weight for a day, preferably distributed over several applications. Exact dosage however depends on a variety of factors including of course patient's nature and condition.

Examples of pharmaceutical preparations for the treatment and control of infections due to yeast, fungi, protozoa and bacteria using compound 25 of the invention as the effective ingredient are provided in the following paragraphs

Example 1. Topical Formulation: Dermal Cream	
Sertaconazole nitrate	0.2-3 g
Benzyl alcohol	1.00 g
2-Octyldodecanol	5.75 g
Liquid paraffin	5.75 g
Stearic alcohol	5.75 g
Cetyl alcohol	5.75 g
Myristhylic alcohol	3.00 g
Tween 60	3.50 g
Span 60	1.50 g
Distilled water s.q.f.	100 g
Example 2. Topical Preparation: Vaginal Cream	
Sertaconazole nitrate	0.2-3 g
Hydrogen ricinus oil	100 mg.
Corn starch	100 mg
Magnesium stearate	6 mg
Microcrystalline cellulose s.q.f.	1 tablet
Example 3. Oral Formulation: Tablets	
Sertaconazole nitrate	200 mg
Corn starch	80 mg
Lactose	160 mg
Polyvinylpyrrolidone	15 mg
Colloidal silicic anhydride	1 mg
Magnesium stearate	2.5 mg
Microcrystalline cellulose s.q.f.	500 mg

Thus, the amount of the compound of formula I, or an acid addition salt thereof, administered to a patient to treat an infection caused by fungi or yeasts on a daily dosage basis amounts to from about 100 mg to about 800 mg. For topical application to treat infections of the skin 0.1 to 5 % of the compound of formula I, or an acid addition salt thereof, in the pharmaceutical carrier is preferably used.

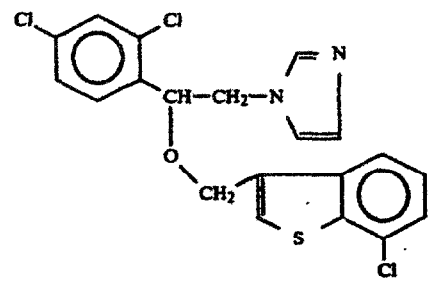
Also the compounds of the present invention, can be used to treat crop diseases caused by fungi or yeasts. The compounds can be administered by watering, atomizing, spraying or dusting, and also in the form of a powder, cream, paste or spray at the rate of 0.1 to 15 kg per hectare.

While the invention has been illustrated and described as embodied in 1H-imidazole derivative compounds and pharmaceutical compositions containing the same for treating infections caused by fungi and yeasts in humans and pets and in crops, it is not intended to be limited to the details shown, since various modifications and structural changes may be made without departing in any way from the spirit of the present invention.

Without further analysis, the foregoing will so fully reveal the gist of the present invention that others can, by applying current knowledge, readily adapt it for various. applications without omitting features that, from the standpoint of the prior art, fairly constitute essential characteristics of the generic or specific aspects of the invention.

We claim:

1. A 1H-imidazole derivative compound of formula I:



(I)

or a nontoxic addition salt thereof.

2. A pharmaceutical composition for treating infections caused by fungi or yeasts in humans and pets, comprising said compound of claim 1 in an effective amount and in combination with a pharmaceutically acceptable carrier.

3. A pharmaceutical composition according to claim 2, in dosage unit form including 100 to 800 mg of said compound.

4. A pharmaceutical composition according to claim 3 for topical application, wherein said compound is present in a concentration from 0.1 to 5 %.

5. A pharmaceutical composition composed of 0.1 to 5 % by weight of said compound of claim 1 in a pharmaceutically acceptable carrier, said compound being present in an amount of from 100 to 800 mg.

6. Method of treating infection caused by fungi or yeast in humans and pet animals, comprising administering an effective amount of the composition according to claim 2.

7. Method of claim 6, wherein said effective amount comprises a daily dose of 100 to 800 mg of said compound.

8. Method of claim 6, wherein said administering comprises oral, injection, rectal, vaginal or topical route administering.

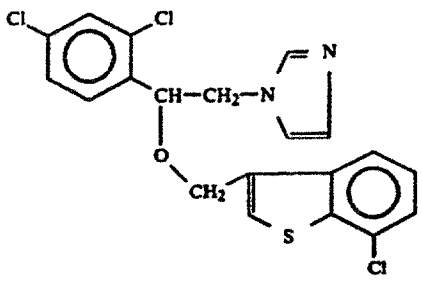
9. Method of treating disease caused by fungi or yeast in crops, comprising applying onto or within the locus of said crops, an effective amount of a compound of claim 1 in combination with carrier means.

10. Method of claim 9, wherein said effective amount comprises 0.1 to 15 kg per hectare of soil.

11. Method of claim 9, wherein said applying comprises watering, atomizing, spraying, dusting or pasting.

12. Compound according to claim 1, wherein said acid addition salt is a nitrate salt.

13. A pharmaceutical composition for treating fungal and yeast infections in humans and pets, comprising 100 to 800 mg of a member selected from the group consisting of a 1H-imidazole derivative compound of formula I:



(I)

and nontoxic addition salts thereof in a pharmaceutically acceptable carrier.

14. A pharmaceutical composition according to claim 13, wherein said nontoxic addition salts include a mononitrate addition salt of said 1H-imidazole derivative compound.

* * * * *

Exhibit 4

United States Patent and Trademark Office

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Maintenance Fee Statement

5135943

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 11, "STAT" below. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,135,943	283	480	0	07/649,764	08/04/92	02/01/91	04	YES	PAID

000000

ITEM NBR	ATTY DKT NUMBER

1

United States Patent and Trademark Office

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Maintenance Fee Statement

5135943

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

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ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,135,943	284	950	0	07/649,764	08/04/92	02/01/91	08	YES	PAID

000000

ITEM NBR	ATTY DKT NUMBER

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United States Patent and Trademark Office

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Maintenance Fee Statement

5135943

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 11, "STAT" below.

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ITEM NBR	PATENT NUMBER	FEE CDE	FEE AMT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,135,943	2553	1610	0	07/649,764	08/04/92	02/01/91	12	YES	PAID

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ITEM NBR	ATTY DKT NUMBER

1

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BOX PATENT EXT.
PATENT
2294-0116M

IN THE U.S. PATENT AND TRADEMARK OFFICE

Patent No.: 5,135,943

Issued: August 4, 1992

Assignee: Ferrer Internacional S.A.

For: 1H-IMIDAZOLE DERIVATIVE COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME

Letter Authorizing Reliance on Activity Before the FDA in Association with Application for Patent Term Extension under 35 U.S.C.§156

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

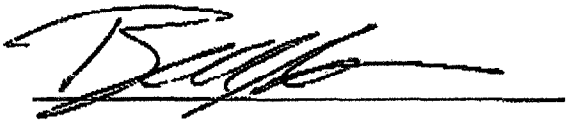
Johnson & Johnson Consumer & Personal Products Worldwide Division of Johnson & Johnson Consumer Companies, Inc. ("JJCP") is the assignee of IND 50,726 and NDA 21-385, filed for the approval of the approved product ERTACZO™ (sertaconazole nitrate) Cream, 2%.

Mylan Pharmaceuticals, Inc. was the marketing applicant before the FDA during the regulatory review period for IND 50,726 and NDA 21-385. During the regulatory review period for IND 50,726 and NDA 21-385, Mylan Pharmaceuticals had an agency relationship with FERRER INTERNACIONAL, S.A., of Barcelona Spain.

This agency relationship was transferred from Mylan Pharmaceutcials, Inc. to JJCP's affiliate Ortho Neutrogena, Division of Ortho-McNeil Pharmaceutical, Inc., following which ownership of IND 50,726 and NDA 21-385 were transferred to JJCP as evidenced by the attached letters from Mylan Pharmaceuticals, Inc. Therefore, since Mylan Pharmaceuticals has transferred its rights and interest in IND 50,726 and NDA 21-385 to JJCP, the undersigned hereby authorizes applicant, FERRER INTERNACIONAL, S.A., to rely on activities before the FDA pursuant to IND 50,726 and NDA 21-385 in association with the approval of ERTACZO™ (sertaconazole nitrate) Cream, 2%.

Very truly yours,

Johnson & Johnson Consumer Companies, Inc.

By: 

William E. McGowan

Assistant Secretary

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

December 22, 2003

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD 540
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
ATTENTION: Central Document Room
9201 Corporate Boulevard
Rockville, MD 20850

TRANSFER OF OWNERSHIP

RE: NDA 21-385; ERTACZO™ (sertaconazole nitrate) CREAM, 2%
Request for Final Approval

Dear Dr. Wilkin:

Reference is made to the New Drug Application (NDA) identified above for ERTACZO™ (sertaconazole nitrate) Cream, 2% that was filed on September 28, 2001 and approved on December 10, 2003. Pursuant to 21 CFR 314.72: Transfer of Ownership, this correspondence will serve as official notification of the Transfer of Ownership of the above referenced New Drug Application.

Effective the date of this letter, ownership and all rights, obligations and responsibilities to the above referenced NDA #21-385, have been transferred from Mylan Pharmaceuticals Inc. to Johnson and Johnson Consumer & Personal Products Worldwide.

A complete copy of the application and records required to be kept under 21 CFR 314 has been provided to Johnson and Johnson. All future correspondence regarding this NDA should be addressed to:

Johnson & Johnson Consumer & Personal Products Worldwide
(Division of Johnson & Johnson Consumer Companies, Inc.)
199 Grandview Road
Skillman, New Jersey 08558-9418

Should you have any questions or require additional clarification about any aspect of this correspondence, please contact the undersigned by phone at (304) 599-2595, ext. 6869 or by telefax at (304) 285-6407.

Sincerely,

Andrea B. Miller, R.Ph., Esq.
Executive Director
Regulatory Affairs

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY
APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
MYLAN PHARMACEUTICALS INC.	December 22, 2003
TELEPHONE NO. *(Include Area Code)* (304) 599-2595	FACSIMILE (FAX) Number *(Include Area Code)* (304) 285-6497
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)* 781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504-4310	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, Telephone & FAX number)* IF APPLICABLE N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued): 21-385

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(Trade name) (if any)*
Sertaconazole Nitrate	Not Assigned

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*
(±)-1-[2,4-Dichloro-β-[(7-chlorobenzo[b]thien-3yl)methoxy]phenethyl]imidazole nitrate

CODE NAME *(if any)*: TX

DOSAGE FORM:	STRENGTHS	ROUTE OF ADMINISTRATION
Cream	2%	Topical

(PROPOSED) INDICATION(S) FOR USE:
The treatment of interdigital tinea pedis caused by dermatophytes

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Holder of Approved Application:

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER OF DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Transfer of Ownership

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

December 22, 2003

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD 540
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
ATTENTION: Central Document Room
9201 Corporate Boulevard
Rockville, MD 20850

TRANSFER OF OWNERSHIP

RE: IND 50,726; SERTACONAZOLE NITRATE CREAM
Serial Number 025

Dear Dr. Wilkin:

Reference is made to the Investigational New Drug Application (IND) identified above for Sertaconazole Nitrate Cream, 2%.

Please be advised that effective the date of this correspondence, ownership and all rights, obligations and responsibilities to the above referenced IND #50,726, have been transferred from Mylan Pharmaceuticals Inc. to Johnson and Johnson Consumer & Personal Products Worldwide.

A complete copy of the application and records required to be kept under 21 CFR 312.20-312.33 has been provided to Johnson and Johnson. All future correspondence regarding this IND should be addressed to:

Johnson & Johnson Consumer & Personal Products Worldwide
(Division of Johnson & Johnson Consumer Companies, Inc.)
199 Grandview Road
Skillman, New Jersey 08558-9418

Should you have any questions or require additional clarification about any aspect of this correspondence, please contact the undersigned by phone at (304) 599-2595, ext. 6869 or by telefax at (304) 285-6407.

Sincerely,

Andrea B. Miller, R.Ph., Esq.
Executive Director
Regulatory Affairs

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Business Development	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 599-3232
		Medical Unit	(304) 598-5445		

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)

Form Approved: OMB No. 0910-0014. Expiration Date: January 31, 2006 See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
MYLAN PHARMACEUTICALS INC.

2. DATE OF SUBMISSION
December 22, 2003

3. ADDRESS (*Number, Street, City, State and Zip Code*)
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. TELEPHONE NUMBER (*Include Area Code*)
(304) 599-2595

5. NAME(S) OF DRUG (*Include all available names: Trade, Generic, Chemical, Code*)
Sertaconazole Cream FI-7056
Sertaconazole Nitrate 91065

6. IND NUMBER (*If previously assigned*)
60,726

7. INDICATION(S) (*Covered by this submission*)
Treatment of tinea pedis and tinea cruris

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED
☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ (Specify)

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR PART 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR PART 314)*, DRUG MASTER FILES *(21 CFR PART 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR PART 601)* REFERRED TO IN THIS APPLICATION.

10. *IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g. amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*

SERIAL NUMBER
0 2 5

11. THIS SUBMISSION CONTAINS THE FOLLOWING: (*Check all that apply*)
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S)
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ Clinical

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☒ OTHER Transfer of Ownership (Specify)

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.36(b) ☐ TREATMENT PROTOCOL 21 CFR 312.36(a) ☐ CHANGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DSIND/DGD RECEIPT STAMP	DDR RECEIPT STAMP	DIVISION ASSIGNMENT:
		IND NUMBER ASSIGNED:

Exhibit 6

CHRONOLOGY OF EVENTS ON ERTACZO (SERTACONAZOLE NITRATE) CREAM 2%. IND #50726;

DATE	EVENT
May 31, 1996	IND submission
June 23, 1997	End of Phase 2 meeting between FDA and Mylan Pharmaceuticals Inc. for IND #50726 Sertaconazole nitrate cream 2%
August 1, 1997	Mylan Pharmaceuticals Inc. submits minutes of the June 23, 1997 EOP2 meeting to IND #59726.
August 1, 1997	Mylan Pharmaceuticals Inc. submits amendment to IND to provide the finalized Phase III protocols.
September 11, 1997	Mylan Pharmaceuticals Inc. submits protocol amendment to the two Phase III protocols along with associated investigator documentation for both studies
October 24, 1997	Mylan Pharmaceuticals Inc. submits protocol amendment to Phase III clinical trial to provide the documentation for new investigator.
October 31, 1997	Mylan Pharmaceuticals Inc. submits IND Annual Report.
November 6, 1998	FDA issues minutes of the End of Phase 2 meeting for IND #50726 Sertaconazole nitrate cream 2%
November 6, 1998	Mylan Pharmaceuticals Inc. receives minutes of the June 23, 1997 EOP2 meeting from the Agency.
August 24, 2000	Mylan Pharmaceuticals Inc. correspondence requesting a Pre-NDA meeting with the Division to discuss the content and format of Mylan's Pharmaceuticals Inc. NDA.
September 29, 2000	Mylan Pharmaceuticals Inc. sends copy of Briefing Package dated September 29, 2000 to discuss with the Division during the October 25, 2000 Pre-NDA meeting.

CHRONOLOGY OF EVENTS ON ERTACZO (SERTACONAZOLE NITRATE) CREAM 2% NDA #21-385

DATE	EVENT
October 18, 2000	Pre-NDA meeting between FDA and Mylan Pharmaceuticals Inc.
September 28, 2001	Mylan Pharmaceuticals Inc. submits Sertaconazole nitrate cream 2% NDA.
November 15, 2001	Mylan Pharmaceuticals Inc. submits CMC and labeling amendment.
November 19, 2001	Teleconference call between the Agency and Mylan Pharmaceuticals Inc.
November 21, 2001	Mylan Pharmaceuticals Inc. submits amendment in response to Agency's telephone request dated November 19, 2001. Submitted document includes data related to the following NDA sections: chemistry, CMC, clinical data, and statistical data.
January 4, 2002	Mylan Pharmaceuticals Inc. submits additional clinical and statistical data in response to the Agency's telephone request dated November 19, 2001.
January 21, 2002	Mylan Pharmaceuticals Inc. submits response to the Agency's November 29, 2001 facsimile transmission requesting additional information on chemistry, clinical and statistical sections.
February 5, 2002	Mylan Pharmaceuticals Inc. submits response to Agency correspondence dated January 15, 2002 and subsequent January 18, 2002 teleconference call between the company and the Agency. Submitted document includes clinical and statistical data.
February 20, 2002	Mylan Pharmaceuticals Inc. submits copies of CMC sections to the Agency for use in inspection of drug substance manufacturer facilities as per e-mail request from the Agency dated January 29, 2002.
March 1, 2002	Mylan Pharmaceuticals Inc. submits response to Agency correspondence dated February 8 and February 22, 2002. Information includes clinical data and requested CRF.
March 7, 2002	Mylan Pharmaceuticals Inc. submits response to the Agency's telephone request on March 7, 2002. Requested data includes replacement pages corresponding to clinical data and CRFs.

March 7, 2002	Mylan Pharmaceuticals Inc. files response to the Agency's February 12, 2002 correspondence. Additional information related to clinical microbiology and clinical data.
April 5, 2002	Mylan Pharmaceuticals Inc. submits response to the Agency's February 26, 2002 facsimile transmission regarding the exposure of pregnant women (or lack thereof) to Sertaconazole nitrate during the conduct of the U.S. clinical trials.
April 19, 2002	Mylan Pharmaceuticals Inc. files response to the Agency's February 14, 2002 correspondence. Document includes clinical and statistical data.
April 24, 2002	Mylan Pharmaceuticals Inc. sends a letter to the Agency to amend application to provide for a proposed market tradename for the drug product.
May 16, 2002	Mylan Pharmaceuticals Inc. submits response to the Agency's correspondence dated April 10, 2002 requesting additional toxicology information.
May 22, 2002	Mylan Pharmaceuticals Inc. submits the NDA Safety Update Report.
July 10, 2002	Mylan Pharmaceuticals Inc. files amendment to include information on the exposure of pregnant woman to Sertaconazole received from Ferrer Internacional, S.A.
July 16, 2002	Mylan Pharmaceuticals Inc. submits response to the Agency's May 29, 2002 facsimile transmission requesting additional clinical microbiology data.
July 26, 2002	FDA issues Action Letter notifying Mylan Pharmaceuticals Inc. that NDA 21-358 ERTACZO ™ (sertaconazole nitrate) cream 2% is "Approvable".
August 21, 2002	Mylan Pharmaceuticals Inc. letter acknowledging receipt of the July 26, 2002 Action Letter and notifying the company decision to file an amendment to address the issues identified in the Action Letter.
October 9, 2003	Mylan Pharmaceuticals Inc. files response to the Agency's July 26, 2002 approvable letter.
October 24, 2003	Mylan Pharmaceuticals Inc. submits response to the Agency's telephone request dated October 17, 2003 requesting an electronic copy of the labeling.
November 24, 2003	Letter from the FDA acknowledging receipt of Mylan's Pharmaceuticals Inc. October 9, 2003 resubmission for ERTACZO ™ (sertaconazole nitrate) cream 2% new drug application. The Agency considers this resubmission as a complete, class I response to July 26, 2002 Action Letter.

December 2, 2003	Mylan Pharmaceuticals Inc. requests a telephone conference with the Division to discuss Phase IV commitments and proposed labeling.
December 5, 2003	Mylan Pharmaceuticals Inc. files submission of negotiated labeling and Phase IV commitments.
December 8, 2003	Mylan Pharmaceuticals Inc. submits a letter of concurrence with draft labeling provided from FDA on December 8, 2003.
December 10, 2003	FDA issues meeting minutes from December 5, 2003 teleconferences concerning NDA 21-385.
December 10, 2003	Action Letter from the FDA approving ERTACZO ™ (sertaconazole nitrate) cream 2% for use as recommended in the agreed-upon labeling text.